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(54) Title: TABLETS CONTAINING EPINASTINE MANUFACTURED BY DIRECT COMPRESSION

(57) Abstract: The invention relates to a tablet manufactured by a direct compression process comprising Epinastine as an active agent with an improved storage stability.

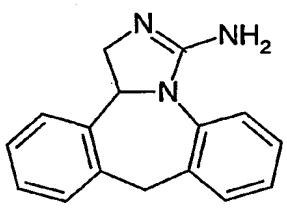
Tablets containing Epinastine manufactured by direct compression

The present invention relates to novel formulations containing Epinastine which show an improved stability during storage.

Background of the invention

Epinastine is a well known drug with antihistaminic properties which is used as an antiallergic or antitussive and *inter alia* for treating the eye and the mucous membrane of the nose. Presently, it is commercially available under the name of Alesion®.

Epinastine, whose chemical name is (±)-3-amino-9,13b-dihydro-1*H*-dibenz-[*c,f*]imidazo[1,5-*a*]-azepine, has the following chemical formula



and was first disclosed in the European Patent EP 35749. Suitable methods for the preparation of Epinastine are described in the European Patents EP 35749 and EP 496306. This compound has been approved for human use and is being sold in many countries around the world. Patent Applications claiming different uses of Epinastine and pharmaceutical compositions comprising Epinastine have also been filed.

One of the most important dosage forms for oral application are tablets. A conventional method for manufacturing tablets is the wet granulation process using water. This method has also been used for the preparation of tablets containing Epinastine.

Epinastine is an amine and as such it is usually formulated in form an pharmaceutically acceptable addition salt, for example in form of the corresponding hydrochloride. On the

other hand, Epinastine is not chemically stable in aqueous solution, especially in the presence of catalytic amounts of acid.

Therefore, when Epinastine hydrochloride is made into tablets by the conventional wet granulation method using water, it generates decomposed compounds during storage, unless the tablets are packaged with an anti-oxygen agent etc. into a moisture-resistant system.

This means that if tablets containing Epinastine are manufactured by wet granulation, the total amount of compounds produced by decomposition and impurities raises rather quickly during storage (see tables 1 and 2). Therefore, even when those tablets are packaged into a moisture-resistent system, i.e. a blister and aluminium bag, addition of an anti-oxygen agent is indispensable.

This low chemical stability of Epinastine containing tablets manufactured by wet granulation is considered to be an important disadvantage in view of the medical and pharmaceutical application of the product.

Summary of the invention

It would be desirable to find a process for manufacturing Epinastine tablets which would guarantee the quality of the tablets even over a long storage period. It would also be appreciated if such tablets could be packaged without addition of an anti-oxygen agent.

The present invention aims to create a tablet containing Epinastine as an active ingredient which can be stored over a prolonged period nearly without decomposition of the active substance, even when it is packaged without addition of an anti-oxygen agent.

Additional to the improvement of stability during storage, the invention aims to simplify the production process by reducing the number of necessary steps for manufacturing the tablets compared to a wet granulation process.

Still another object of the invention is to create a tablet containing a combination of Epinastine and one or more other OTC drugs as active substances which has the same improved storage stability.

Description of the invention

The invention relates to a process for preparing tablets containing Epinastine, reliably and on a commercial scale, which comprises formulating the tablets in the absence of water, without the use of a wet granulation process.

Surprisingly, it has been found that the decomposition during storage is markedly reduced when a direct compression process is employed for manufacturing the Epinastine tablets. Furthermore, experiments show that the storage stability of Epinastine hydrochloride can only be improved by employing a direct compression method, but not by any other manufacturing method.

The present invention relates to a tablet comprising Epinastine as active agent, one or more filling and/or disintegrating agents, lubricants and optionally coloring agents which is produced by direct compression. The invention also relates to such tablets which additionally to Epinastine contain one or more other active agents selected from the group of OTC drugs such as for example Belladonna extract.

Direct compression is a dry process which avoids the use of water. It should be understood that the term "dry" means "substantially dry" as opposed to the wholesale addition of water which was previously employed in the wet granulation process.

Another advantage of the manufacture by direct compression is that the number of process steps could be reduced compared to the wet granulation method. At least process steps such as granulation with granulation liquid and drying are not necessary. Especially drying is a highly energy-consuming production step. Therefore, costs would be markedly reduced by using the direct compression process.

With the direct compression method, the present invention discloses a process for preparing Epinastine tablets that is energy-, cost- and labor-saving. This is of special interest for producing Epinastine tablets of uniform quality in a commercial scale.

Direct compression techniques are generally known in the art of pharmaceutical science. For example, Epinastine is conventionally admixed with dry excipients and compressed into tablets.

Additional excipients, like carriers and vehicles, may then be added and mixed with the free flowing powder before being compressed into tablets.

Examples of excipients include lactose, starch, preferably corn starch, magnesium stearate, polyvinylpyrrolidone, for example Polyvinylpyrrolidone K25, light anhydrous silicic acid, cellulose, preferably hydroxypropylmethylcellulose, most preferably Hydroxypropylmethyl-cellulose 2910, methacrylic acid copolymer, Macrogol 6000, glycerol esters of fatty acids, talc, titanium oxide and silicone.

Preferably, non dried corn starch is used.

The preferred excipients used for preparing the core tablets are lactose, starch, magnesium stearate, polyvinylpyrrolidine and light anhydrous silicic acid.

The tablets may also comprise any other pharmacologically acceptable additive for tablets well known in the art.

The Epinastine/excipients mixture may be compressed into an appropiate tablet shape. Preferred shapes include oval, round bi-convex or round with bevelled edges. Round bi-convex tablets with bevelled edges are preferred.

Epinastine when incorporated into the above-mentioned tablets is suitably present as the hydrochloride form which may for example be prepared according to the procedures outlined in the European Patent EP 496306.

The amount of Epinastine hydrochloride present in the above-mentioned tablets is in the range of 5 to 50 mg. Particularly preferred amounts include 10 and 20 mg of Epinastine hydrochloride.

Alternatively, Epinastine may be incorporated into the tablets in form of other physiologically acceptable addition salts with various mineral or organic acids. Examples for suitable acids are phosphoric acid, sulfuric acid, methanesulfonic acid, p-toluenesulfonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, mandelic acid, malic acid, citric acid, tartaric acid or maleic acid.

After the tablets have been compressed, these core tablets may optionally be film-coated. The film-coating serves to mask a bitter taste of the tablets and to prevent photo degradation. The film-coating can also be used for additional improvement of the stability of the tablets, especially to prevent discoloration. The tablets are preferably of white color.

The film-coated tablets are preferred compared to the non-film-coated tablets.

The film-coating may for example be proceeded using water, or using a mixture of water and an additional liquid such as alkyl-alcohol, preferably isopropanol, as a medium and cellulose derivatives such as for example hydroxypropylmethylcellulose, methacrylic acid copolymer, Macrogol, glycerol esters of fatty acids, talc, titanium oxide or silicone as film-coating material.

Surprisingly, manufacturing the core tablets by a direct compression method reduces the decomposition during storage of the film-coated tablets, even when the film-coating is proceeded using water as a medium.

An useful procedure for preparing a lot of tablets according to the method disclosed in this specification is outlined in the following as an example:
Epinastine hydrochloride, non-dried corn-starch and light anhydrous silicic acid are sieved using a suitable dry sieving apparatus to obtain a mixture with a suitable distribution of particle sizes. Then lactose and Polyvinylpyrrolidone K25 are added to the sieved mixture and the resulting mixture is mixed in a suitable positive mixer to be uniform. Then, magnesium stearate is added and all ingredients are mixed finally. In the following tableting step, the final mixture is compressed on a suitable rotary tableting press to give tablets of the desired weight, size and shape.

Afterwards, the core tablets may be film-coated using a film-coating suspension which is prepared in several steps and consists of an aqueous solution of hydroxy-propylmethylcellulose, an emulsion of silicone in isopropanol, Macrogol 6000, talc, titanium oxide, methacrylic acid copolymer and purified water. Alternatively, Macrogol 6000 can be replaced with glycerol esters of fatty acids. The use of glycerol esters of fatty acids prevents the discoloration of the film-coat. The final coating suspension is used for coating the preheated tablet cores to give the coated tablets of the desired specification. The coating process is effected under specified conditions in a suitable coating pan with an automatic spray system.

The present invention also relates to tablets containing Epinastine and one or more other OTC drugs as active substances. Those tablets may be prepared by a direct compression process as described above. An additional OTC drug used for manufacturing those combination tablets may for example be Belladonna extract.

Experimental Data

The following examples are destianted to illustrate the invention. The scope of the invention shall not be limited to the examples.

With respect to tables 1 and 2, the two kinds of tablets, manufactured either by a wet granulation or by a direct compression process, did not differ in terms of product moisture and decomposition content just after manufacturing. To be precise, the active substance, i.e. Epinastine hydrochloride, used for manufacturing both kinds of tablets contained 0.1 to 0.3 % of decomposed material and the fresh made tablets did contain, before storing, 0.3 to 0.6 % of decomposed material if they were manufactured by wet granulation and 0.2 to 0.3 % when manufactured by direct compression.

Both kind of tablets were packaged into a moisture-resistant system consisting of a blister and an aluminium-bag. Unless noted otherwise, the tablets manufactured by wet granulation were packaged with an anti-oxygen agent, but those produced by direct compression were packaged without such an anti-oxygen agent. The anti-oxygen agent which was used is the

oxygen absorber Type Z-100 manufactured by Mitsubishi gas chemical Co., Ltd, which is an active ferric oxide.

Long term stability conditions mean a storage at temperature of 25 °C and a relative humidity (RH) of 60 to 75 %; accelerated stability conditions refer to a temperature of 40 °C and a relative humidity of 75 %.

However, as shown in tables 1 and 2, the rate of decomposition was clearly different between the two kind of tablets after storage. The effect is beyond the expectation and in contrast to the general understanding that the decomposition rate of the product is affected by its residual moisture.

Table 1: Total related compounds (decomposition and impurities) for tablets containing 10 mg Epinastine hydrochloride (Example 1)

Storage conditions	Storage period	Wet granulation	Direct compression
Long-term stability	12 months	1.2 – 1.5 %	0.3 – 0.5 %
Long-term stability	24 months	1.2 – 1.5 %	0.4 – 0.6 %
Long-term stability	36 months	---	0.5 – 0.6 %
Accelerated stability	3 months	---	0.4 – 0-6 %
Accelerated stability	6 months	1.4 –1.7 %	0.5 – 0.7 %
Accelerated stability	6 months	1.8 – 3.8 % (without an anti-oxygen agent)	0.5 – 0.7 %

Table 2: Total related compounds (decomposition and impurities) for tablets containing 20 mg Epinastine hydrochloride (Example 2)

Storage conditions	Storage period	Wet granulation	Direct compression
Long-term stability	12 months	---	ca. 0.5 %
Long-term stability	24 months	---	0.4 – 0.5 %
Long-term stability	36 months	---	ca. 0.5 %
Accelerated stability	3 months	1.3 – 1.6 %	ca. 0.5 %
Accelerated stability	6 months	1.5 – 1-7 %	ca. 0.5 %

Example 1

Constituents:

Core tablet	mg/tablet
Epinastine hydrochloride	10.0
Lactose	41.4
Corn starch	31.0
Polyvinylpyrrolidone K25	0.8
Light anhydrous silicic acid	1.3
Magnesium stearate	0.5
Subtotal	85.0

Film coat	
Hydroxypropylmethylcellulose 2910	0.3430
Methacrylic acid copolymer	0.3850
Macrogol 6000	0.4280
Talc	1.3696
Titanium oxide	0.4710
Silicone	0.0034
Volatile constituents:	
Purified water	16.97
Isopropanol	0.0306
Total	88.0

The resulting core tablets have a weight of between 81.0 and 93.0 mg and an average weight of about 87 mg (before preheating), a diameter of 6.0 to 6.1 mm, a thickness of 2.75 to 2.95 mm and a hardness of more than 2.5 kp. They are round bi-convex with bevelled edges and their color is white.

The film coated tablets have an average weight of about 88 mg and are round in shape with bevelled edges. Their diameter ranges between 6.0 and 6.2 mm and their thickness between 2.80 and 3.00 mm. They are white.

Example 2

Constituents

Core tablet	mg/tablet
Epinastine hydrochloride	20.0
Lactose	82.8
Corn starch	62.0
Polyvinylpyrrolidone K25	1.6
Light anhydrous silicic acid	2.6
Magnesium stearate	1.0
Subtotal	170.0

Film coat	
Hydroxypropylmethylcellulose 2910	0.5708
Methacrylic acid copolymer	0.6421
Macrogol 6000	0.7135
Talc	2.2831
Titanium oxide	0.7848
Silicone	0.0057
Volatile constituents:	
Purified water	28.27
Isopropanol	0.0513
Total	175.0

The resulting core tablets have a weight of between 162.0 and 186.0 mg and an average weight of about 174 mg (before preheating), a diameter of 8.0 to 8.1 mm, a thickness of 3.15 to 3.45 mm and a hardness of more than 2.5 kp. They are a round bi-convex with bevelled edges and their color is white.

The film coated tablets have an average weight of about 175 mg and are round in shape with bevelled edges. Their diameter ranges between 8.0 and 8.2 mm and their thickness between 3.15 and 3.50 mm. They are white.

In each case non-dried corn starch was used.

The hardness of the tablets was measured by the "Schleuniger Tablet Hardness Tester". The hardness of the tablets means the crushing strength.

Claims

1. A process for preparing tablets containing Epinastine, reliably and on a commercial scale, which comprises formulating the tablets without a wet granulation process of epinastine.

2. A process according to claim 1 wherein the tablets are manufactured by a direct compression process.

3. A process according to claim 1 characterized in that
   a) a physiologically acceptable addition salt of Epinastine is admixed with the excipients,
   b) the final mixture is compressed into tablets and
   c) the core tablets are optionally film-coated.

4. A process according to claim 3 wherein the physiologically acceptable addition salt of Epinastine is Epinastine hydrochloride.

5. A process according to any one of the claims 1 to 4 wherein Epinastine is admixed with one or more excipients selected from the group consisting of diluents, binders, disintegration enhancers, anti-adherents and lubricants.

6. A process according to one of the claims 3 to 5 wherein the film-coating material comprises coating excipients, pigments and antifoaming agents.

7. A process according to one of the claims 3 to 6 wherein the excipients used for preparing the core tablets are selected from the group consisting of lactose, starch, polyvinylpyrrolidone, silicic acid and magnesium stearate.

8. A process according to one of the claims 3 to 7 wherein the film-coating material is selected from the group consisting of magnesium stearate, cellulose, methacrylic acid, Macrogol 6000, talc, titanium oxide and silicone.

9. A process according to claim 8 wherein Macrogol 6000 is replaced by glycerol esters of fatty acids.

10. A process according to any one of the claims 3 to 9 in which the film-coating is carried out using water or water in admixture with one or more additional liquids, such as alkyl-alcohols, as solvents.

11. A process according to any one of the claims 1 to 10 wherein the amount of Epinastine hydrochloride present in each tablet ranges between 5 and 50 mg.

12. A process according to one of the claims 1 to 11 in which each tablet is compressed into a round bi-convex shape with bevelled edges.

13. A process according to any one of the claims 1 to 12 in which the tablets contain 10 mg of Epinastine hydrochloride each.

14. A process according to any one of the claims 1 to 12 in which the tablets contain 20 mg of Epinastine hydrochloride each.

15. A process according to one of the claims 1 to 14 for preparing tablets containing a combination of Epinastine and one or more OTC drugs as active compounds.

16. A process according to claim 15 wherein the OTC drug is Belladonna Extract.

17. A tablet formulation obtainable by a process according to any one of claims 1 to 16.

18. Use of the tablet according to claim 17 as an antiallergic or antihistamine.

INTERNATIONAL SEARCH REPORT

ional Application No
PCT/EP 01/10139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 1 000 623 A (BOEHRINGER INGELHEIM) 17 May 2000 (2000-05-17) claim 1 page 5; example 1	1-3,5, 11-14,17 4,6-8, 10,18
P,Y	CHEMICAL ABSTRACTS, vol. 134, Columbus, Ohio, US; abstract no. 242689, SAKIYAMA, SHIGERU ET AL: "Light-resistant film-coated tablets of epinastine-HCl" XP002188389 abstract & JP 2001 081033 A (TOWA YAKUHIN K. K., JAPAN) 27 March 2001 (2001-03-27)	4,6,8, 10,18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 19 54 281 A (BOEHRINGER INGELHEIM) 16 July 1970 (1970-07-16) page 6, line 13 - line 20	7
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INTERNATIONAL SEARCH REPORT

Information on patent family members

I						tional Application No	
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